CLAIMS

1. A pharmaceutical composition comprising a therapeutically active antisense oligonucleotide construct which (i) comprises at least one locked nucleic acid unit selected from the group consisting of amino-LNA and thio-LNA and derivatives thereof; or (ii) comprises at least two consecutively located locked nucleotide units of which at least one is selected from the group consisting of alpha-L-oxy-LNA and derivatives thereof.

2. A pharmaceutical composition according to claim 1, in which the antisense oligonucleotide construct comprises two adjacently located nucleotide sequences A and B, where

A represents a sequence of nucleotide units comprising (i) at least one locked nucleotide unit selected from the group consisting of thio-LNA, amino-LNA (both in either alpha-L or beta-D configuration) and derivatives thereof, or (ii) at least two consecutively located locked nucleotide units of which at least one is selected from the group consisting of alpha-L-oxy-LNA and derivatives thereof; and

B represents one nucleotide unit or a sequence of nucleotide units, with the proviso that at least one nucleotide unit in B has a 2'-deoxy-erythro-pentofuranosyl sugar moiety or a ribo-pentofuranosyl sugar moiety.

3. A pharmaceutical composition according to claim 2, in which sequence A additionally comprises at least one further locked nucleotide unit (such as 2, 3, 4 or 5 units), preferably selected independently from the group consisting of amino-LNA, thio-LNA (both in either alpha-L or beta-D configuration), alpha-L-oxy-LNA and derivatives thereof.

4. A pharmaceutical composition according to any of claims 1-2, comprising an oligonucleotide construct which contains three adjacently located nucleotide sequences, A, B and C, in the following order (5' to 3'):

A-B-C or C-B-A,

in which

A represents a sequence comprising at least two consecutively located locked nucleotide units, at least one of which is an alpha-L-oxy-LNA unit, and which sequence optionally contains one or more (such as 2, 3, 4 or 5) non-locked nucleotide units (such as deoxyribonucleotide units, ribonucleotide units or derivatives thereof) and/or optionally contains one or more (such as 2, 3, 4 or 5) locked nucleotide units, such as a unit selected from the group consisting of oxy-LNA, thio-LNA, amino-LNA (all in either alpha-L or beta-D configuration) and derivatives thereof;

B represents one nucleotide unit or a sequence of nucleotide units, with the proviso that at least one nucleotide unit in B has a 2'-deoxy-erythro-pentofuranosyl sugar moiety or a ribo-pentofuranosyl moiety; and

C represents a sequence comprising at least two consecutively located locked nucleotide units, at least one of which is an alpha-L-oxy-LNA unit, and which sequence optionally contains one or more (such as 2, 3, 4 or 5) non-locked nucleotide units (such as deoxyribonucleotide units, ribonucleotide units or derivatives thereof) and/or optionally contains one or more (such as 2, 3, 4 or 5) locked nucleotide units, such as a unit selected from the group consisting of oxy-LNA, thio-LNA, amino-LNA (all in either alpha-L or beta-D configuration) and derivatives thereof.

5. A pharmaceutical composition according to any of claims 2-4, in which B represents a sequence of nucleotide units that makes the construct able to recruit RNase H when hybridised to a target nucleic acid.

6. A pharmaceutical composition according to any of claims 1-5, in which the linkages between the nucleotide units in the oligonucleotide construct independently are selected from the group consisting of -O-P(O)$_2$-O-, -O-P(O,S)-O-, -O-P(S)$_2$-O-, -NR^H-P(O)$_2$-O-, -O-P(O,NR^H)-O-, -O-PO(R")-O-, -O-PO(CH$_3$)-O-, and -O-PO(NHR^N)-O-, where R^H is selected form hydrogen and C$_{1-6}$-alkyl, and R" is selected from C$_{1-6}$-alkyl and phenyl.

7. A pharmaceutical composition according to any of claims 2-6, in which the linkages between the nucleotides in sequence B in the oligonucleotide construct comprises at least one linkage which is not a -O-P(O)$_2$-O- linkage, such as a phoshorothioate linkage.

8. A pharmaceutical composition according to any of claims 1-7, which further comprises a pharmaceutical carrier.

9. A pharmaceutical compostion according to any of claims 1-8, which further comprises other antisense compounds, chemotherapeutic compounds, antiinflammatory compounds and/or antiviral compounds.

10. An oligonucleotide construct which comprises at least one nucleotide sequence comprising one or more nucleotide units selected from the group consisting of amino-LNA, thio-LNA and derivatives thereof;
with the proviso that the following oligonucleotide constructs are excluded:
(i) 5'-d(GTGAVATGC), 5'-d(GVGAVAVGC), 5'-d(GTGAXATGC), 5'-d(GXGAXAXGC), 5'-d(GXGVXVXGC), in which sequences V represents a beta-D-amino-LNA thymine unit, and X represents a beta-D-methylamino-LNA thymine unit; and

(ii) 5'-d(GTGAYATGC), 5'-d(GYGAYAYGC) and 5'-d(GYGYYYYGC) in which sequences Y represents a beta-D-thio-LNA uracil unit.

11. An oligonucleotide construct according to claim 10, which comprises two adjacently located nucleotide sequences, A and B, where
A represents a sequence of nucleotide units comprising at least one locked nucleotide unit selected from the group consisting of amino-LNA, thio-LNA (both in either alpha-L or beta-D) configuration, and derivatives thereof; and
B represents one nucleotide unit or a sequence of nucleotide units, with the proviso that at least one nucleotide unit in B has a 2'-deoxy-erythro-pentofuranosyl sugar moiety or a ribo-pentofuranosyl moiety.

12. An oligonucleotide construct according to any of claims 10-11, which comprises two adjacently located nucleotide sequences, A and B, where
A represents a sequence of nucleotide units comprising at least one locked nucleotide unit selected from the group consisting of amino-LNA, thio-LNA and derivatives thereof; and
B represents a sequence of nucleotide units, said sequence contains a subsequence of at least three nucleotide units having 2'-deoxy-erythro-pentofuranosyl sugar moieties, such as 4, 5, 6, 7, 8, 9 or 10 nucleotide units, said subsequence optionally being spiked with an other nucleotide, preferably an alpha-L-oxy-LNA unit selected from the group consisting of alpha-L-amino-LNA, alpha-L-thio-LNA, alpha-L-oxy-LNA and derivatives thereof.

13. A construct according to claim 11-12, comprising the two adjacently sequences in the following order (5' to 3'):

A-B or B-A.

14. A construct according to claim 10-13, which comprises three adjacently located nucleotide sequences in the following order (5' to 3'):

A-B-C,

in which the nucleotide sequences A and B are as defined in any of claims 11-13, and C represents a sequence of nucleotide units, which comprises at least one locked nucleotide unit selected from the group consisting of amino-LNA, thio-LNA (both in either alpha-L or beta-D configuration) and derivatives thereof.

15. A construct according to any of claims 11-14, which is selected from the group consisting of (in 5' to 3' order):

A-B, B-A and A-B-C, where
A, B, and C have the same meaning as defined in claims 11-14, and where
A has a length of 2-10 (preferably 2-8) nucleotide units;
B has a length of 1-10 (preferably 5-8) nucleotide units;
C (if present) has a length of 2-10 (preferably 2-8) nucleotide units; and the overall length of the construct is 6-30 (preferably 10-20, more preferably 12-18) nucleotide units.

16. A construct according to any of claims 11-15, in which A represents a sequence of nucleotide units comprising at least two consecutively located locked nucleotide units (such as 3, 4, 5, 6, 7, 8, 9 or 10 units), at least one of said locked nucleotide units being selected from the group consisting of amino-LNA, thio-LNA and derivatives thereof.

17. A construct according to any of claims 11-16, in which C represents a sequence of nucleotide units comprising at least two consecutively located locked nucleotide units (such as 3, 4, 5, 6, 7, 8, 9 or 10 units), at least one of said locked nucleotide units being selected from the group consisting of amino-LNA, thio-LNA and derivatives thereof.

18. A construct according to any of claims 11-17, in which B represents a sequence of least 2 nucleotide units (such as 3, 4, 5, 6, 7, 8, 9 or 10 units), which sequence in addition to the nucleotide unit(s) having 2'-deoxy-erythro-pentofuranosyl sugar moiety(ies) and/or ribo-pentofuranosyl moiety(ies), comprises nucleotides units which are selected independently from the group consisting of: locked nucleotide units (such as alpha-L-oxy-, -thio-, or -amino- nucleotide units) and derivatives thereof.

19. A construct according to any of claims 10-18, wherein the linkages between the nucleotide units in the oligonucleotide construct independently are selected from the group consisting of -O-P(O)$_2$-O-, -O-P(O,S)-O-, -O-P(S)$_2$-O-, -NR^H-P(O)$_2$-O-, -O-P(O,NR^H)-O-, -O-PO(R")-O-, -O-PO(CH$_3$)-O-, and -O-PO(NHR^N)-O-, where R^H is selected form hydrogen and C$_{1-6}$-alkyl, and R" is selected from C$_{1-6}$-alkyl and phenyl.

20. A construct according to any of claims 11-19, in which the linkages between the nucleotides in sequence B comprises at least one linkage which is not a -O-P(O)$_2$-O- linkage, such as a phoshorothioate (-O-P(O,S)-O-) linkage.

21. An oligonucleotide construct according to any of claims 11-20, in which
B represents a sequence of nucleotide units that makes the construct able to recruit RNase H when hybridised to a target nucleic acid.

22. An oligonucleotide construct which contains three adjacently located nucleotide sequences, A, B and C, in the following order (5' to 3'):
A-B-C or C-B-A,
in which
A represents a sequence comprising at least two consecutively located locked nucleotide units, at least one of which is an alpha-L-oxy-LNA unit, and which sequence optionally contains one or more (such as 2, 3, 4 or 5) non-locked nucleotide units (such as deoxyribonucleotide units, ribonucleotide units or derivatives thereof) and/or optionally contains one or more (such as 2, 3, 4 or 5) locked nucleotide units, such as a unit selected from the group consisting of oxy-LNA, thio-LNA, amino-LNA (all in either alpha or beta configuration) and derivatives thereof;
B represents one nucleotide unit or a sequence of nucleotide units, with the proviso that at least one nucleotide unit in B has a 2'-deoxy-erythro-pentofuranosyl sugar moiety or a ribo-pentofuranosyl moiety; and
C represents a sequence comprising at least two consecutively located locked nucleotide units, at least one of which is an alpha-L-oxy-LNA unit, and which sequence optionally contains one or more (such as 2, 3, 4 or 5) non-locked nucleotide units (such as deoxyribonucleotide units, ribonucleotide units or derivatives thereof) and/or optionally contains one or more (such as 2, 3, 4 or 5) locked nucleotide units, such as a unit selected from the group consisting of oxy-LNA, thio-LNA, amino-LNA (all in either alpha or beta configuration) and derivatives thereof.

23. A construct according to claim 22, in which the three adjacently located nucleotide sequences are in the following order (5' to 3'):
A-B-C.

24. A construct according to any of claims 22-23, which has the formula (in 5' to 3' order):

A-B-C, where

A, B, and C have the same meaning as defined in any of claims 22-23, and where
A has a length of 2-10 (preferably 2-8) nucleotide units;
B has a length of 1-10 (preferably 5-8) nucleotide units;
C has a length of 2-10 (preferably 2-8) nucleotide units; and the overall lenght of the construct is 8-30 (preferably 10-20) nucleotide units.

25. A construct according to any of claims 22-24, in which A represents a sequence of nucleotide units comprising at least three consecutively located locked nucleotide units, at

least one of said locked nucleotide units being selected from the group consisting of alpha-L-oxy-LNA and derivatives thereof.

26. A construct according to any of claims 22-25, in which C represents a sequence of nucleotide units comprising at least three consecutively located locked nucleotide units, at least one of said locked nucleotide units being selected from the group consisting of alpha-L-oxy-LNA and derivatives thereof.

27. A construct according to any of claims 22-26, in which B represents a sequence of least 2 nucleotide units (such as 3, 4, 5, 6, 7, 8, 9 or 10 units), which sequence in addition to the nucleotide unit(s) having 2'-deoxy-erythro-pentofuranosyl sugar moiety(ies) and/or ribo-pentofuranosyl moiety(ies), comprises nucleotides units which are selected independently from the group consisting of: locked nucleotide units (such as alpha-L-oxy-, -thio-, or -amino- nucleotide units) and derivatives thereof.

28. A construct according to any of claims 22-27, wherein the internucleoside linkages independently are selected from the group consisting of -O-P(O)$_2$-O-, -O-P(O,S)-O-, -O-P(S)$_2$-O-, -NR^H-P(O)$_2$-O-, -O-P(O,NR^H)-O-, -O-PO(R")-O-, -O-PO(CH$_3$)-O-, and -O-PO(NHR^N)-O-, where R^H is selected form hydrogen and C$_{1-6}$-alkyl, and R" is selected from C$_{1-6}$-alkyl and phenyl.

29. A construct according to any of claims 22-28, in which B comprises at least one internucleotide linkage which is not a -O-P(O)$_2$-O- linkage, such as a phoshorothioate linkage.

30. A construct according to any of claims 22-29, in which B comprises at least one locked nucleotide unit selected from the group consisting of alpha-L-oxy-LNA and derivatives thereof.

31. A construct according to any of claims 22-30, in which A and C comprises at least one alpha-L-oxy-LNA or alpha-L-thio-LNA unit located adjacent to B.

32. An oligonucleotide which has the formula (in 5' to 3' order):

A-B-C-D, in which

A represents a sequence of locked nucleotide units;

B represents a sequence of non-locked nucleotide units, preferably at least one unit has a 2'-deoxy pentofuranose sugar moiety, in which sequence 1 or 2 nucleotide units optionally are substituted with locked nucleotide units, preferably alpha-L-oxy-LNA;
C represents a sequence of locked nucleotide units; and
D represents a non-locked nucleotide unit or a sequence of non-locked nucleotide units.

33. A construct according to any of claims 32, which has the formula (in 5' to 3' order):

A-B-C-D, where

A, B, and C have the same meaning as defined in claim 32, and where
A has a length of 2-6 (preferably 3-5) nucleotide units;
B has a lenght of 4-12 (preferably 6-10) nucleotide units;
C has a length of 1-5 (preferably 2-4) nucleotide units;
D has a lenght of 1-3 (preferably 1-2) nucleotide units; and the overall length of the construct is 8-26 (preferably 12-21) nucleotide units.

34. A construct according to any of claims 32-33, in which
A has a length of 4 nucleotide units;
B has a length of 7-9, preferably 8, nucleotide units;
C has a length of 3 nucleotide units;
D has a length of 1 nucleotide unit; and the overall length of the construct is 15-17 (preferably 16) nucleotide units.

35. A construct according to any of claims 32-34, in which the locked nucleotide units in A and C are beta-D-oxy-LNA units.

36. A construct according to any of claims 32-35, wherein the internucleoside linkages independently are selected from the group consisting of -O-P(O)$_2$-O-, -O-P(O,S)-O-, -O-P(S)$_2$-O-, -NR^H-P(O)$_2$-O-, -O-P(O,NR^H)-O-, -O-PO(R")-O-, -O-PO(CH$_3$)-O-, and -O-PO(NHR^N)-O-, where R^H is selected form hydrogen and C$_{1-6}$-alkyl, and R" is selected from C$_{1-6}$-alkyl and phenyl.

37. A construct according to any of claims 32-36, in which B comprises at least one internucleotide linkage which is not a -O-P(O)$_2$-O- linkage, such as a phoshorothioate linkage.

38. An oligonucleotide construct according to any of claims 32-37, in which

B represents a sequence of nucleotide units that makes the construct able to recruit RNase H when hybridised to a target nucleic acid.

39. An oligonucleotide construct which comprises at least one locked nucleotide unit selected from the group consisting of amino-LNA, thio-LNA (both in either alpha-L or beta-D configuration), alpha-L-oxy-LNA, and derivatives thereof;
wherein at least one of the linkages between the nucleotide units is selected from the group consisting of -O-P(O,S)-O-, -O-P(S)$_2$-O-, -NR^H-P(O)$_2$-O-, -O-P(O,NR^H)-O-, -O-PO(R")-O-, -O-PO(CH$_3$)-O-, and -O-PO(NHR^N)-O-, where R^H is selected form hydrogen and C$_{1-6}$-alkyl, and R" is selected from C$_{1-6}$-alkyl and phenyl.

40. A construct according to any of claims 39, which comprises at least one phoshorothioate internucleoside linkage.

41. A construct according to any of claims 39-40, which comprises a subsequence of nucleotide units, said nucleotide units having 2'-deoxy-erythro-pentofuranosyl sugar moieties.

42. A method of synthesis of a pharmaceutical composition or constructs according to any of the claims 1-42.